PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/335 — A1

(11) International Publication Number: **WO 97/41850**

(43) International Publication Date: 13 November 1997 (13.11.97)

(21) International Application Number: PCT/KR96/00183

(22) International Filing Date: 26 October 1996 (26.10.96)

(30) Priority Data:
1996/14189 2 May 1996 (02.05.96) KR

(71)(72) Applicant and Inventor: SONG, Yeong, Wook [KR/KR]; Dept. of Internal Medicine, College of Medicine, Seoul National University, 28, Yungun-dong, Chongro-ku, Seoul 110-744 (KR).

(72) Inventors; and

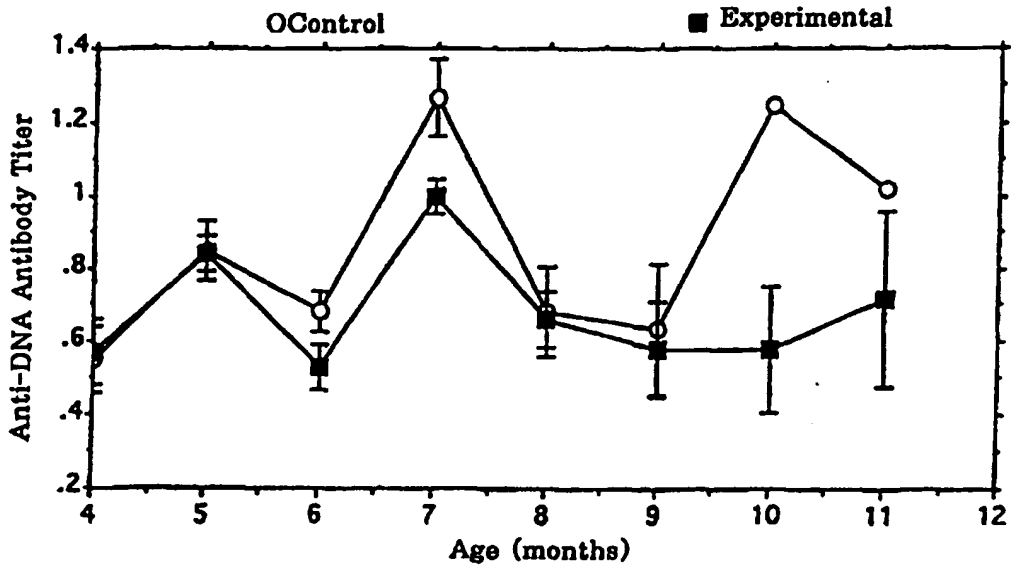
(75) Inventors/Applicants *(for US only)*: HONG, Kyung, Man [KR/KR]; 27-710 Samho Apartment, Wolgye-3-dong, Nowon-ku, Seoul 139-053 (KR). CHUNG, Eun, Sook [KR/KR]; 4-201 Miju Apartment, Chongryang-1-dong, Dongdaemun-ku, Seoul 130-011 (KR).

(74) Agent: LEE, Kuiy, Dong; Seoul Building, 114-31, Uni-dong, Chongro-ku, Seoul 110-350 (KR).

(81) Designated States: AU, CA, CN, HU, JP, MX, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: PACLITAXEL FOR THE TREATMENT OF RHEUMATIC DISEASES



(57) Abstract

Paclitaxel has been found to have a potential effect on the protection against the development of rheumatic disease. Therefore, paclitaxel is supposed to be a potential agent for the treatment of rheumatic diseases, especially systemic lupus erythematosus (SLE).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

PACLITAXEL FOR THE TREATMENT OF RHEUMATIC DISEASES

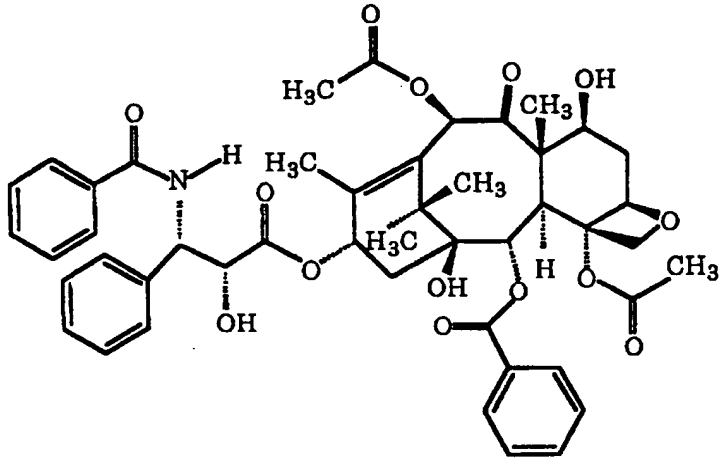
BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a novel use of paclitaxel for the treatment of rheumatic diseases. More particularly, the invention relates to the use of paclitaxel for the treatment of systemic lupus erythematosus (SLE).

2. Description of the Prior Art

Paclitaxel belongs to the taxane family of compounds. It has the chemical name of 5β,20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine and the following structural formula:



Paclitaxel, which is commercially available under the trade name of TAXOL, has been known and used as an anti-cancer agent, especially for ovarian and breast cancers. The cytotoxic effects of this compound is based on its unique mechanism which promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This leads to disruption of normal microtuble dynamics required for cell division and vital interphase processes which culminate in cell death: *See* Schiff P. B. *et al.*, 1979, "Promotion of microtubule

assembly *in vitro* by taxol," 1979, Nature 277:665-667; and Rowinsky E. K. *et al.*, "Paclitaxel," 1995, New England Journal of Medicine 332(15):1004-1014.

Paclitaxel has also been shown to enhance interleukin-β and tumor necrosis factor-α(TNF-α) production. In relation to this property of paclitaxel, several reports indicate the role of TNF-α in the development of autoimmune diseases and the replacement therapy for the treatment of the diseases. Jacob C. O. *et al.* presented evidence that TNF-α could be involved in the pathogenesis of lupus nephritis in (NZB X NZW) F_1 mice, an animal model of autoimmune disease in "Tumor necrosis factor-α in murine autoimmune lupus nephritis," 1988, Nature, 331(28):356-137. Hiroshi Ishida *et al.* suggested that the protection by the anti-interleukin 10 antibodies against autoimmunity is due to an anti-IL-10-induced upregulation of endogenous TNF-α in "Continuous administration of anti-interleukin 10 antibodies delays the onset of autoimmunity in NZB/W F_1 mice," 1994, J. Exp. Med. 179:305-310.

Paclitaxel has also been found to completely preclude the development of rheumatoid arthritis and also suppress the established clinical disease in an animal model: *See* Brahn E. *et al.* "Regression of collagen induced arthritis with taxol, a microtubule stabilizer," 1994, Arthritis Rhreum., 37(6):839-845. This effect was shown to be augmented further by the addition of an angiogenesis inhibitor: *See* Oliver S. J. *et al.*, "Suppression of collagen-induced arthritis using an angiogenesis inhibitor, AGM-1470, and a microtubule stabilizer, taxol," Cellular Immunolology, 157:291-299. The mechanism of action of these agents was postulated to be multifold including inhibition of mitosis and chemotaxis of the inflammatory cells, inhibition of antigen processing and presentation by the macrophage, inhibition of angiogenesis and so forth, which are core mechanisms of pathogenesis of many autoimmune diseases.

However, none of the studies and reports described above provide or suggest any possibility of paclitaxel being succesfully used to manage and treat rheumatic diseases including systemic lupus erythematosus (SLE).

The inventors of the present application have studied on the effect of paclitaxel in the treatment of rheumatic disease based on the several characteristic mechanisms of rheumatic disease pathogenesis and found that paclitaxel improved the clinical

course of murine lupus after development of autoimmunity. Although it is uncertain at present whether changes in TNF-α levels or effects on microtubule polymerization, or both provided the most benefit in the case concerned, paclitaxel improved the survival rate of the animals which is undoubtedly due to the decreased anti-dsDNA antibody titer and the blood urea nitrogen (BUN).

SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide a paclitaxel preparation which has a potential effect in the treatment of rheumatic disease. The paclitaxel preparation is particularly effective for the treatment of systemic lupus erythematosus (SLE) which is found to have the highest mortality among systemic rheumatic diseases.

Further objects and advantages of the invention will become apparent through reading the remainder of the specification.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the survival rates of paclitaxel treated and control groups of mice as a function of the duration of the treatment.

Figure 2 is a graph showing the change of the blood urea nitrogen (BUN) as a function of the duration of the treatment.

Figure 3 is a graph showing the change of proteinuria as a function of the duration of the treatment.

Figure 4 is a graph showing the change of serum anti-dsDNA antibody titer as a function of the duration of the treatment.

DETAILED DESCRIPTION OF THE INVENTION

The potential effect of paclitaxel on the protection against the development of rheumatic diseases, especially systemic lupus erythematosus (SLE), was proved using (NZB X NZW) F_1 hybrids, an animal model of systemic lupus erythematosus in

humans.

Systemic lupus erythematosus (SLE) is a chronic and systemic kind of rheumatic diseases which primarily attack the tissue and blood system including connective tissue. Although the pathogenesis of this disease is not yet fully known, many studies suggest that it is a disease of an autoimmune reaction which is generated by an antibody to its own tissue.

While eleven standard examinations for the diagnosis of SLE are established by the American Rheumatism Association, several basic diagnostic examinations are generally conducted: for example, a blood examination in general including measurement of the erythrocyte, leucocyte and platelet counts, urinalysis (measurement of proteinuria), examinations for kidney function and chest X-rays and cardiac ultrasound examinations.

Among these diagnostic methods, serum anti-dsDNA antibody titer, complement concentration in the blood, proteinuria, serum creatinine concentration, erythrocyte sedimentation rate, and leucocyte and platelet counts are important and useful for the observation of the clinical course and the anticipated activity of the disease. Protein in urine (proteinuria) indicates an attack into the kidney and varies depending on the activity of the disease. Blood urine nitrogen (BUN) is also an indication of kidney function. An increase in BUN implies deterioration of kidney function while a decrease in BUN implies its improvement. Thus, BUN is a very useful tool for evaluating the reaction to a treatment agent. Finally, anti-dsDNA antibody is the most specific antibody which can be found in SLE cases. Thus, it could be a definite indication for the diagnosis of the disease and the effect of the treatment agent as well.

For the clinical use according to the present invention, paclitaxel can be formulated into a parenteral preparation. A solution for injection is particularly preferred. A paclitaxel solution preparation can be prepared, for example, by dissolving paclitaxel in a pharmaceutically acceptable solvent in an appropriate concentration (preferably 0.1 to 10%) and, if necessary, with stabilizers and/or buffering solutions. Paclitaxel solution for injection can be distributed in ampules or vials with different doses. Alternatively, paclitaxel can be formulated into a parenteral dry preparation which can be reconstituted with a suitable solvent before

use.

Dosage of paclitaxel can be varied in a wide range depending on the type and severity of disease, administration route and individual requirements of a patient. For intravenous injections, an effective daily dosage is 7.5mg/m^2 to 15mg/m^2 of body surface area. The daily dosage is generally administered over a five day period in a week and this administration pattern can be repeated for four weeks, and possibly for 6 to 12 months depending on the severity of the disease.

In lethality studies, Sprague-Dawley rats were intraperitoneally administered a paclitaxel injection solution once a day for 1 day or once a day for 5 days, while CD2F$_1$ mice were treated once a day for 5 days. Doses lethal to 10%, 50%, and 90%(LD_{10}, LD_{50}, and LD_{90}, respectively) of the rats given a single dose were 138, 206, and 307 mg/m^2, respectively. The LD_{10}, LD_{50}, and LD_{90} for rats treated once a day for 5 days were 36, 51 and 74 mg/m^2 per day, respectively, whereas corresponding values in mice were 70, 82 and 97 mg/m^2 per day.

To address the effect of paclitaxel on the severity of the autoimmunity, we carried out a series of experiments as follows.

1. Animal Model

New Zealand Black X New Zealand White (NZB X NZW) F$_1$ female mice were purchased from Harlan-Sprague Dawley. This strain is known to develop a severe autoimmune disease culminating in death from nephritis by 1 year of age: *See*, Theofilopoulus A. N. *et al.*, "Murine models of systemic lupus erythematosus," 1985, Advanced Immunology 37:269. These models develop some immunological features similar to systemic lupus erythematosus in humans which includes antibodies to dsDNA antigens and the subsequent development of immune complex-mediated glomerulonephritis. Treatment was started when the mice reached 5 months of age.

2. Treatment with Paclitaxel

A paclitaxel sample, TAXOL was purchased from Bristol-Myers Squibb, Princeton, New Jersey. Taxol was initially solubilized in a 1:1 dilution of ethanol and Cremophor EL (Sigma). Normal saline was added to make a final concentration

of 2.4 mg/ml taxol in 5%(w/v) ethanol and 5%(w/v) Cremophor EL, prior to administration by intraperitoneal injection. A total of 35 mice were divided into two groups; one group of 15 mice was a treatment group and the other group of twenty mice was the control group. The treatment group was injected intraperitoneally with the taxol solution at a dose of 10mg/kg every other day for 6 days, and this treatment was followed by the same route and pattern of administration except that the dose was reduced to 7.5mg/kg. This two-step administration pattern was repeated every fourth week for 6 months. For the purpose of comparison, the same volume of vehicle containing 5% ethanol and 5% Cremophor in normal saline was administrated to the control group of 20 mice in the same manner.

3. Assesment

Survival rate: Survival rates in each group were calculated by the Kaplan Meier method for Individual periods of treatment through out followup and compared by the log-rank test.

Renal disease: The development of renal disease was assessed by the appearance and level of the proteinuria and by elevation of the BUN. Proteinuria was measured colorimetrically using dipsticks (Albustix; Miles laboratories, Inc., Elkhart, IN) and was graded as follows: trace, 10mg/dl; 1+, 30mg/dl; 2+, 100mg/dl; 3+, 300mg/dl; and 4+, 1,000mg/dl. BUN was measured by azostix(Milas Laboratories).

Anti-dsDNA antibody : Serum antibodies specific for double stranded DNA were quantified by ELISA as described in Zouali M., B. D. Stollar, 1986, "A rapid ELISA for measurement of antibodies to nucleic acids antigens using UV-treated polystyrene microlates," J. Immunol. Methods. 90:105.

Fluorescene analysis of lymphocytes subpopulations: Periperal blood was obtained from individual mice by retroorbital bleeding into heparinized pipets. Mononuclear cells were separated by centrifugation over Lymphocyte-M (Cedarlane Laboratories, Ontario, Canada) and quantified using a Coulter ZBI cell counter. Mononuclear subsets were identified by staining with fluoroscein-conjugated monoclonal antibody (mAb), as described in Seaman W. E. *et al.*, "Treatment of autoimmune MRL lpr/lpr mice with monoclonal antibody to Thy-1.2: a single injection sustained effects on lymphoproliferation and renal diseases," Journal

Immunology 130:1713. The antibodies used for analysis included: anti-CD4 to identify helper T cell subsets, CD8 to identify suppressed T cell subsets and B220. Fluoroscein isothiocyanate(FITC) conjugated rat anti-mouse CD4 and B220 mAb, phycoerythrin(PE) conjugated rat anti-mouse CD8 mAb were used to detect anti-CD4 on target cell surfaces. Fluoroscein analysis was performed immediately prior to the initiation of the treatment.

Stastical analysis: Means, standard deviation (SD) and standard error of mean (SEM) were calculated by standard method. A one factor analysis of variance (ANOVA) for repeated measures was used for continuous variables for significance of differences between the two groups. Results were considered to be at the confidence level of 90% or higher.

4. Results and Discussions

As can be seen from Figure 1, 80% of the vehicle treated mice died between 38 and 144 days and the survival pattern did not differ from that of untreated control mice as reported previously. On the other hand, half of the paclitaxel treated mice were alive after 160 days of observation ($p=0.04$ by log-rank test). There was no evidence of hypersensitivity reaction in either of the groups. Thus, the administration of paclitaxel prolonged the survival of the (NZB X NZW) F_1 mice.

In Figure 2, while the degree of proteinuria appeared to be less in the experimental group, the difference reached only the 82% confidence level by ANOVA for repeated measurement which is not so significant. BUN was also significantly diminished in paclitaxel treated group compared to the vehicle treated animals(Figure 3). This implies that kidney function has been improved by the treatment with paclitaxel. Thus, the diminution in the impairment of renal function as reflected by the serum BUN may very likely have been the cause for the increased survival of the paclitaxel treated (NZB X NZW) F_1 mice.

In Figure 4, anti-dsDNA antibody titers were significantly diminished in paclitaxel treated group compared to the vehicle treated animals. This also demonstrates that the clinical course of SLE could be improved by paclitaxel treatment.

What Is Claimed Is:

1. A preparation for treatment of rheumatic diseases comprising an effective dosage of paclitaxel and suitable excipients.

2. The preparation of Claim 1 wherein said rheumatic disease is systemic lupus erythematosus.

3. The preparation of Claim 1 which is a solution for injection.

4. The preparation of Claim 1 comprising paclitaxel in a concentration of 0.1 to 10%(w/v).

FIG. 1

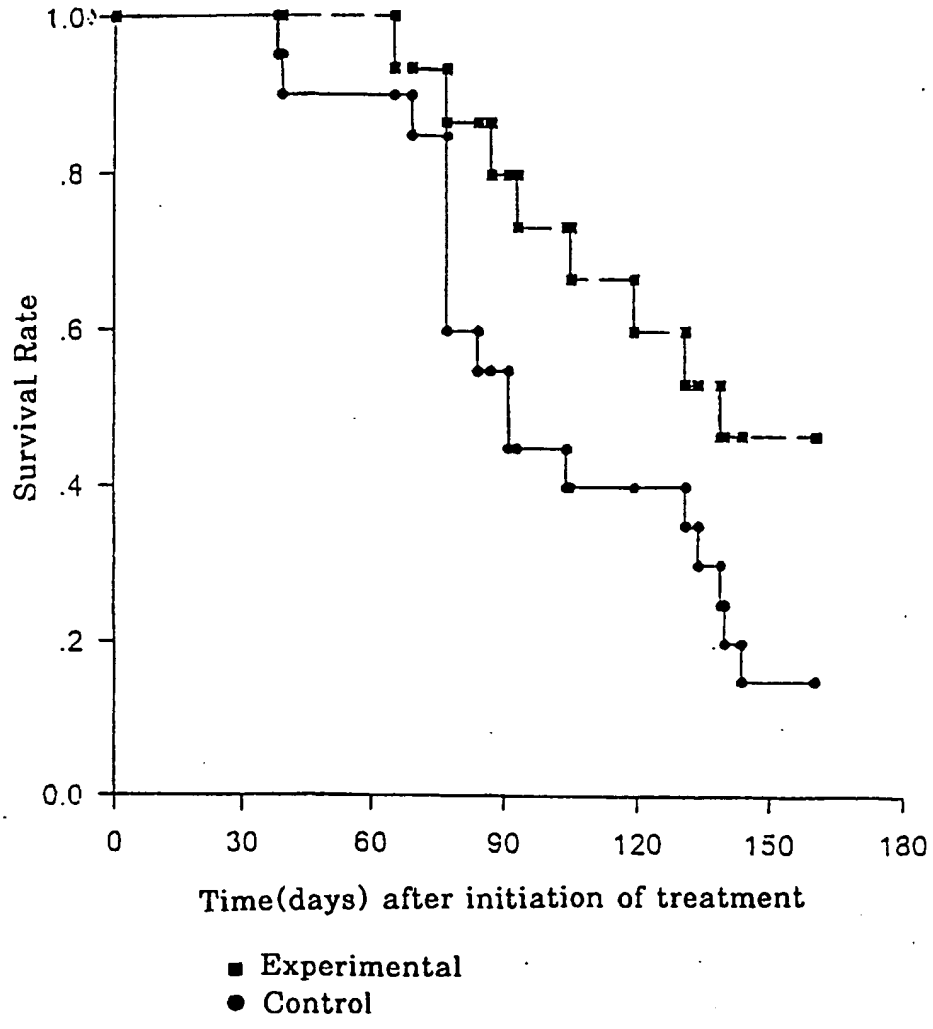

1.0
.8
.6
.4
.2
0.0
Survival Rate
0
30
60
90
120
150
180
Time(days) after initiation of treatment
Experimental
Control

FIG. 2

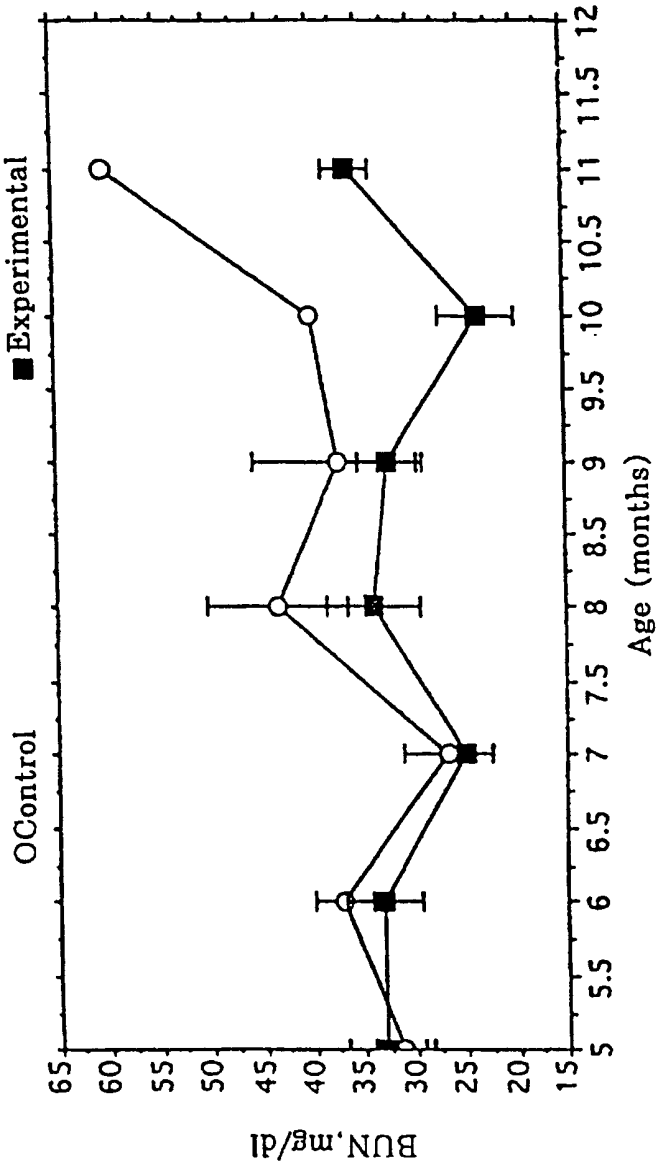

BUN, mg/dl
65
60
55
50
45
40
35
30
25
20
15
5
5.5
6
6.5
7
7.5
8
8.5
9
9.5
10
10.5
11
11.5
12
Age (months)
OControl
■Experimental

FIG. 3

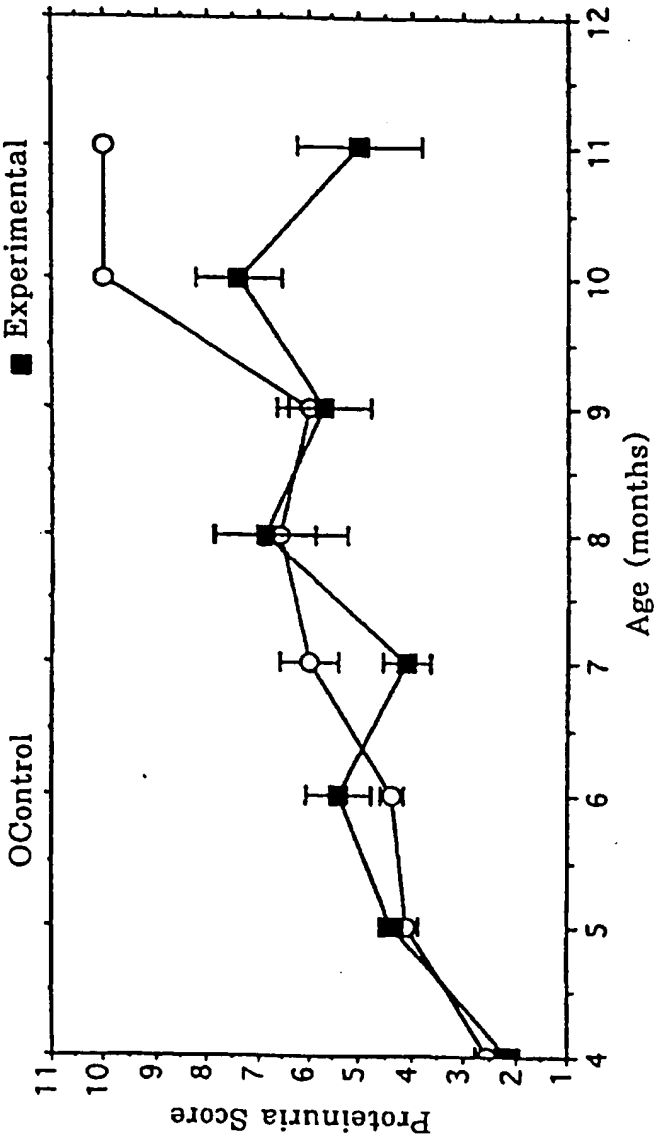
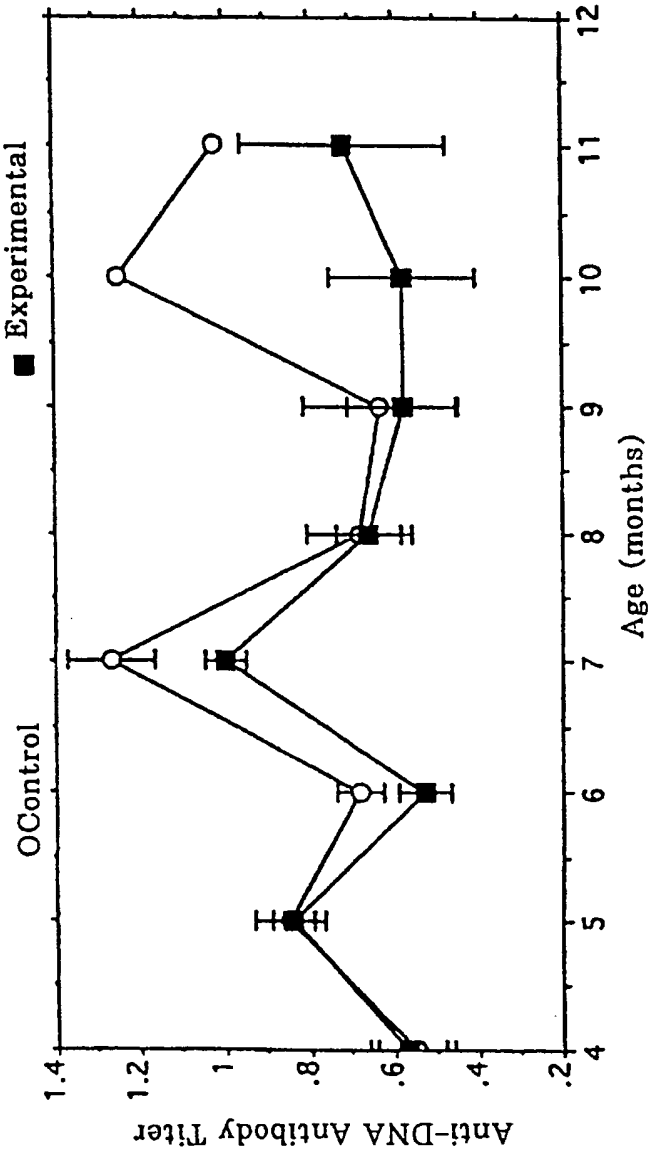

Experimental
OControl
Proteinuria Score
Age (months)
1
2
3
4
5
6
7
8
9
10
11
12

FIG. 4


Experimental
OControl
Anti-DNA Antibody Titer
Age (months)
1.4
1.2
1
.8
.6
.4
.2
4
5
6
7
8
9
10
11
12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 96/00183

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: A 61 K 31/335

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel (FI CAS, FI WPIL)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93/00 928 A1 (RHONE-POULENC RORER S.A.) 21 January 1993 (21.01.93), abstract, claims 1,4-7.	1-4
X	WO 94/12 171 A1 (RHONE-POULENC RORER S.A.) 09 June 1994 (09.06.94), abstract; claims 1,2,4-7,9.	1-4
X	WO 94/12 172 A1 (THOMAS JEFFERSON UNIVERSITY) 09 June 1994 (09.06.94), abstract; claims 1,7,10; page 9, line 15 - page 10, line 20.	1-4
X	WO 94/12 198 A1 (F.H.FAULDING & CO. LTD.) 09 June 1994 (09.06.94), abstract; claims 1,2,8,12.	1-4
X	Chemical Abstracts, Vol.106, No.22, 01 June 1987 (Columbus, Ohio, USA), page 405, column 1, abstract No.182581c, B.D. TARR et al.:"A new parenteral vehicle for the administration of some poorly water soluble anti-cancer drugs", & J. PARENTER. SCI. TECHNOL., 41(1), 31-3 (Eng).	1-4
A	BRAHN e. et al.:"Regression of Collagen-Induced Arthritis with Taxol, a microtubule Stabilizer"; Arthritis & Rheumatism, June 1994, Volume 37, No.36,	1-4

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 January 1997 (08.01.97)	21 January 1997 (21.01.97)

Name and mailing address of the ISA/ AT	Authorized officer
AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna	Mazzucco
Facsimile No. 1/53424/535	Telephone No. 1/5337058/33

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 96/00183

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	pp. 839-845, abstract,(cited in the application).	
A	OLIVER S.J. et al.:"Suppression of Collagen-Induced Arthritis Using an Angiogenesis Inhibitor, AGM-1470, and a Microtubule Stabilizer, Taxol"; Cellular Immunology, August 1994, Volume 157, No.1, pp. 291-299, abstract, (cited in the application).	1-4

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 96/00183

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO A1 9300928	21-01-93	AU A1 22787/92	11-02-93
		AU B2 666859	29-02-96
		CZ A3 9400032	15-02-95
		CZ B6 280965	15-05-96
		EP A1 522936	13-01-93
		EP A1 522937	13-01-93
		EP A1 593601	27-04-94
		EP A1 593656	27-04-94
		FI A 940073	07-01-94
		FI A 940074	07-01-94
		FI A0 940073	07-01-94
		FI A0 940074	07-01-94
		FR A1 2678833	15-01-93
		FR B1 2678833	07-04-95
		HU A0 9400052	30-05-94
		HU A2 65960	29-08-94
		JP T2 6507913	08-09-94
		JP T2 6507914	08-09-94
		MX A1 9203959	02-03-93
		MX A1 9203960	02-03-93
		NO A 934609	14-12-93
		NO A 934610	14-12-93
		NO A0 934609	14-12-93
		NO A0 934610	14-12-93
		PL B1 169372	31-07-96
		SK A3 15/94	05-10-94
		US A 5403858	04-04-95
		WO A1 9300928	21-01-93
		ZA A 9204999	28-04-93
WO A1 9412171	09-06-94	AU A1 55669/94	22-06-94
		CA AA 2150576	09-06-94
		CN A 1090170	03-08-94
		CZ A3 9501421	18-10-95
		EP A1 671912	20-09-95
		FI A 952680	01-06-95
		FI A0 952680	01-06-95
		FR A1 2698543	03-06-94
		FR B1 2698543	30-12-94
		HU A0 9501596	28-08-95
		HU A2 72650	28-05-96
		JP T2 8503689	23-04-96
		NO A 952151	31-05-95
		NO A0 952151	31-05-95
		NZ A 258150	26-11-96
		PL A1 309197	18-09-95
		SK A3 725/95	08-11-95
		US A 5438072	01-08-95
		ZA A 9308936	03-08-94
WO A1 9412172	09-06-94	AU A1 57350/94	22-06-94
		US A 5356927	18-10-94
WO A1 9412198	09-06-94	AU A1 51967/93	09-06-94
		AU A1 55538/94	22-06-94
		AU A1 56126/94	22-06-94
		AU B2 667142	07-03-96
		CA AA 2149150	09-06-94
		CN A 1095266	23-11-94
		CN A 1096673	28-12-94
		EP A1 674510	04-10-95
		JP T2 8503945	30-04-96
		NZ A 258044	21-12-95
		WO A1 9412030	09-06-94
		WO A1 9412031	09-06-94
		ZA A 9308844	02-08-94